PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07C 275/28, A61K 31/17 | A2

(11) International Publication Number: **WO 00/61546**

(43) International Publication Date: 19 October 2000 (19.10.00)

(21) International Application Number: PCT/CA00/00413

(22) International Filing Date: 12 April 2000 (12.04.00)

(30) Priority Data:
2,268,588 12 April 1999 (12.04.99) CA

(71) Applicant *(for all designated States except US)*: UNIVERSITE LAVAL [CA/CA]; Pavillon des Sciences de l'Education, local 1442, Cité universitaire, Ste-Foy, Quebec G1K 7P4 (CA).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: GAUDREAULT, René, C. [CA/CA]; 2102, Chemin Aubin, St-Nicolas, Quebec G7A 2N3 (CA).

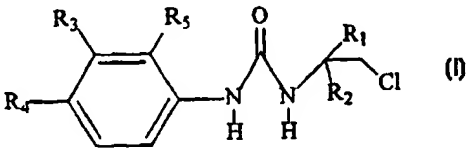
(74) Agents: DUBUC, Jean, H. et al.; Goudreau Gage Dubuc, The Stock Exchange Tower, Suite 3400, 800 Place Victoria, Montreal, Quebec H4Z 1E9 (CA).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

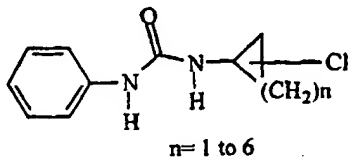
Published

Without international search report and to be republished upon receipt of that report.

(54) Title: NOVEL ARYL-CHLORO-ETHYL UREAS

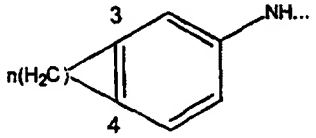


(I)



(II)

n= 1 to 6



(III)

(57) Abstract

Described herein are novel 1-aryl-3-(2-chloroethyl)ureas derivatives. These derivatives are useful anticancer agents having excellent specify towards cell targets and potent antineoplastic activity without systemic toxicity or mutagenicity. More specifically, the invention is directed to novel derivatives of formula (I), wherein R_1 is C_1-C_6 lower alkyl, C_3-C_7 cycloalkyl, C_1-C_6 lower alkoxy, C_1-C_6 hydroxy alkyl, or C_1-C_6 lower halide; R_2 is H, C_1-C_6 lower alkyl, C_3-C_7 cycloalkyl, C_1-C_6 lower alkoxy, C_1-C_6 hydroxy alkyl or C_1-C_6 lower halide, di-halide or tri-halide; R_1 and R_2 may also be part of cyclic structures expressed by formula (II), R_3 and R_4 are as defined in R_5 or, halide, di-halide, trihalide, C_1-C_7 lower dialkyl, or alicyclic groups of structure (III), wherein n = 2 to 8 carbon atoms, said alicyclic ring can be substituted by one or more groups as defined in R_5; or polycyclic rings bearing not more than three rings wherein the rings other than the ring bearing the substituted 2-chloroethylamino moiety can be substituted by one or more groups as defined in R_5; R_5 is H, C_1-C_7 lower alkyl, C_1-C_7 lower alkoxy, C_1-C_7 hydroxy alkyl, C_1-C_7 amino alkyl, C_1-C_6 thio alkyl, C_1-C_5 S-lower alkyl, C_1-C_7 N-lower alkyl, C_1-C_7 N,N-dilower alkyl, C_1-C_7 lower cyanoalkyl, C_1-C_7 lower haloalkyl, C_1-C_7 lower sulfoxide or C_3-C_7 cycloalkyl; or a prodrug thereof. Also disclosed are pharmaceutical compositions containing the compounds of the invention in conjunction with a pharmaceutically acceptable carrier and the use of the compositions in treating cancer.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

TITLE OF THE INVENTION: NOVEL ARYL-CHLORO-ETHYL UREAS

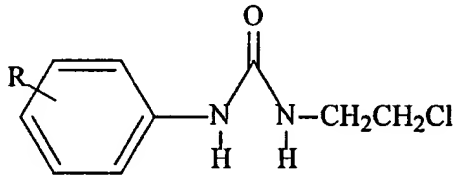
BACKGROUND OF THE INVENTION

1. Field of Invention

This invention relates to novel anticancer agents having potent antineoplastic activity without systemic toxicity or mutagenicity. Moreover, the compounds of the present invention present higher specificity to cancer cell targets than previously known compounds. The present invention also relates to pharmaceutical compositions comprising at least one compound of the present invention as active agent. More specifically, the invention is directed to novel derivatives of 1-aryl-3-(2-chloroethyl)ureas having substituents on the first carbon atom of the 2-chloroethyl moeity.

2. The Prior Art

Some 1-aryl-3-(2-chloroethyl)urea derivatives (hereinafter referred to as "CEUs") are known from US Patents 5,530,026 and 5,750,547 to the same assignee as the present application. More specifically, compounds of the following formula are known:



wherein R refers to various substituents on the phenyl ring.

It is known that CEUs display an affinity towards cancer cells, permeate the cell wall and provide a mild alkylating effect on cell components thereby killing the offending cell.

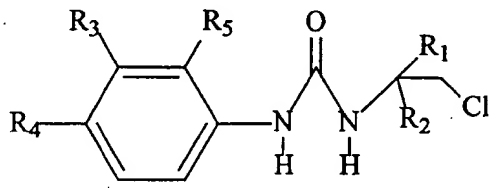
An object of the invention is to provide novel CEU derivatives having significantly superior antineoplastic activity over known CEUs while maintaining low systemic toxicity, mutagenicity and side-effects.

SUMMARY OF THE INVENTION

It has now been found, against expectations and documented precedents that specific substitutions on the first carbon atom of the 2-chloroethyl group of the CEU molecule provides a significant improvement on the anticancer effect of the resulting CEU.

Moreover, it has been found that yet unknown substitutions on the phenyl ring render the resulting CEU molecule even more efficient at targeting specific regions of cancerous cells thereby improving their specificity toward various cellular proteins key to cell survival.

More specifically, this invention provides a novel class of CEU derivatives. This novel class of CEU may be expressed by the following formula:



wherein

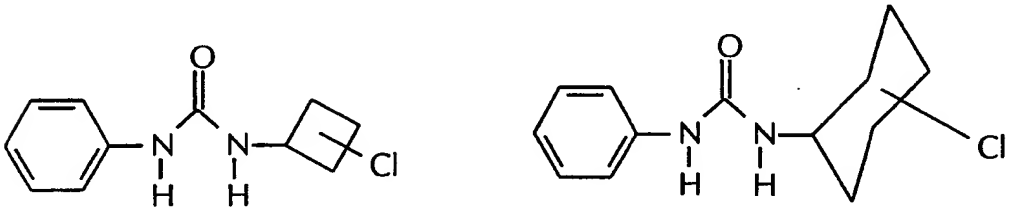
R_1 is lower alkyl (1 to 6 carbon atoms) or
cycloalkyl (3 to 7 carbon atoms) or
lower alkoxy or hydroxy alkyl (1 to 6 carbon atoms)
lower halide, lower di-halide or lower tri-halide (Br, I, Cl, F) (1 to 6 carbon atoms)

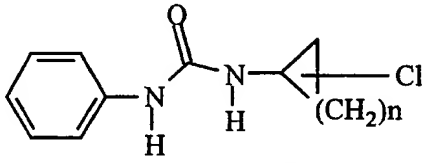
R_2 is H or
lower alkyl (1 to 6 carbon atoms) or
cycloalkyl (3 to 7 carbon atoms) or
lower alkoxy or hydroxy alkyl (1 to 6 carbon atoms)

lower halide, lower di-halide or lower tri-halide (Br, I, Cl, F) (1 to 6 carbon atoms)

R_1 and R_2 could also be part of cyclic structures expressed by the formula:

examples:





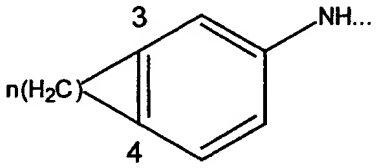
n= 1 to 6

R_3 and R_4 are as defined in R_5, or halide, dihalide or trihalide (e.g. CF_3)

lower dialkyl (1 to 8 carbon atoms)

in R_3 and R_4, (the number of carbon atoms present is not necessarily identical ("asymetric molecules")) or

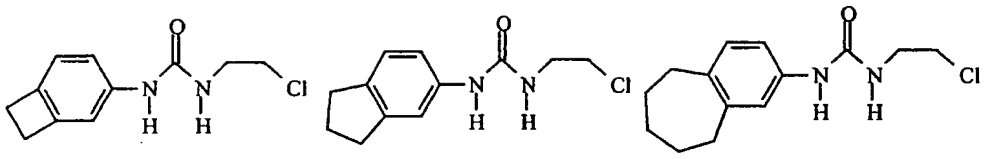
alicyclic groups of the following structures



wherein n = 2 to 8 carbon atoms,

The alicyclic ring could also be substituted by one or more substituting groups comprising groups as described for R_5

R_3 and R_4 can also be polycyclic rings bearing not more than three rings such as dihydrophenanthrene, anthracene, phenanthrene, fluorenyl, etc., examples:



wherein the rings other than the ring bearing the substituted 2-chloroethylamino moiety can be substituted by one or more groups as defined in R_5.

R_5 is H or

lower alkyl (1 to 7 carbon atoms) or

lower alkoxy or hydroxy alkyl , amino alkyl, thio alkyl (1 to 7 carbon atoms) or

S-lower alkyl

N-lower alkyl

N,N-dilower alkyl

lower cyanoalkyl (1 to 7 carbon atoms)

cycloalkyl (3 to 7 carbons atoms)

lower haloalkyls (Br, I, Cl, F) (1 to 7 carbon atoms)

lower sulfoxides (1 to 7 carbon atoms)

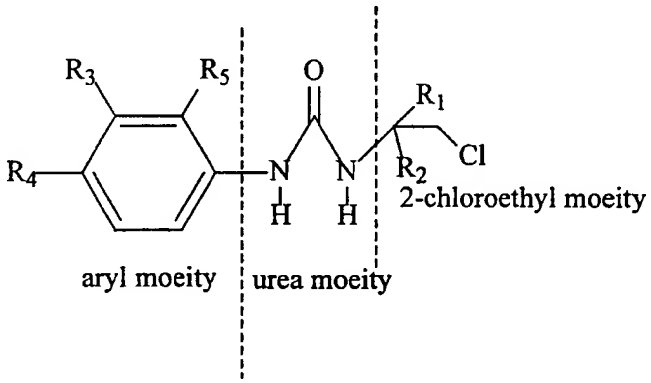
Further scope of applicability of the present invention will become apparent from the detailed description given hereinafter. It should be understood, however, that this detailed description, while indicating preferred embodiments of the invention, is given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

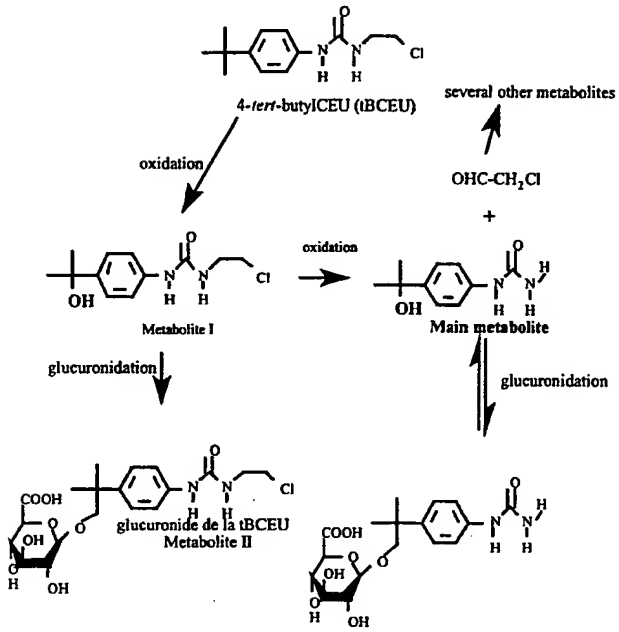
Before describing the present invention in detail, it is to be understood that the invention is not limited in its application to the details of the preferred embodiments and examples described herein. The invention is capable of other embodiments and of being practised in various ways. It is also to be understood that the phraseology or terminology used herein is for the purpose of description and not limitation.

MODIFICATION OF THE 2-CHLROETHYL MOIETY (R_1 and R_2 groups)

Experiments to assess the biopharmaceutical properties of known 1-aryl-3-(2-chloroethyl) ureas (CEUs) have unexpectedly revealed that certain cell enzymes such as cytochromes P_{450} 1A2 and 2E1 were oxidizing CEUs therefore metabolizing them to inert molecules and depriving them of anticancer effect. The metabolization mechanism was again unexpectedly found to operate on the first carbon atom on the chloro-2-ethyl moiety adjacent to the urea moiety.



For example, in the case of a 4-*tert*-butyl CEU (*t*BCEU), metabolization occurred along the following pathway:



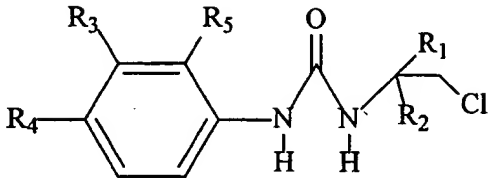
Surprisingly this has revealed a metabolic weak spot at the first carbon atom of the 2-chloro-ethyl moiety of the CEUs. Thus, the present invention generally aims at providing protecting groups on this first carbon atom and at providing novel CEU derivatives having potent antineoplastic activity.

More specifically, the protection of the weak carbon atom from metabolization was achieved by substituting the hydrogen atoms with groups such as lower alkyl groups such as methyl, ethyl and propyl.

MODIFICATION OF THE R_3, R_4 AND R_5 MOIETIES

Furthermore, it was surprisingly discovered that certain modifications of substituents on the aryl moiety dramatically improved the specificity of the resulting CEU derivatives toward various cellular proteins key to cell survival.

Thus, the following compounds were developed and are expressed by the general formula:

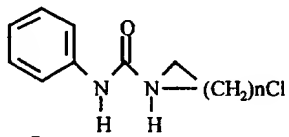


wherein

R_1 is lower alkyl (1 to 6 carbon atoms) or
cycloalkyl (3 to 7 carbon atoms) or
lower alkoxy or hydroxy alkyl (1 to 6 carbon atoms)
lower halide, lower di-halide or lower tri-halide (Br, I, Cl, F) (1 to 6 carbon atoms)

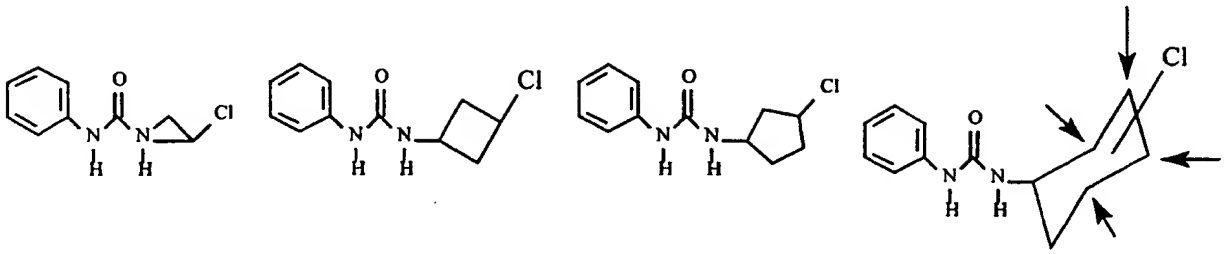
R_2 is H or
lower alkyl (1 to 6 carbon atoms) or
cycloalkyl (3 to 7 carbon atoms) or
lower alkoxy or hydroxy alkyl (1 to 6 carbon atoms)
lower halide, lower di-halide or lower tri-halide (Br, I, Cl, F) (1 to 6 carbon atoms)

R_1 and R_2 can be part of cyclic structures expressed by the formula:



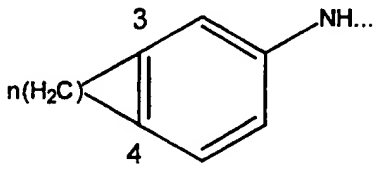
n= 1 to 5

Such as:

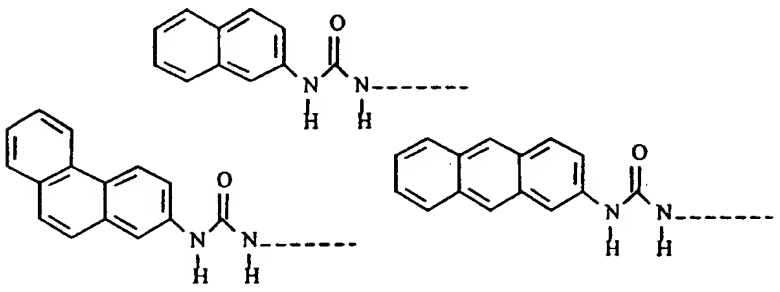


wherein the arrows on the molecule on the right hand side indicate the position where the molecule can be substituted by the chlorine atom;

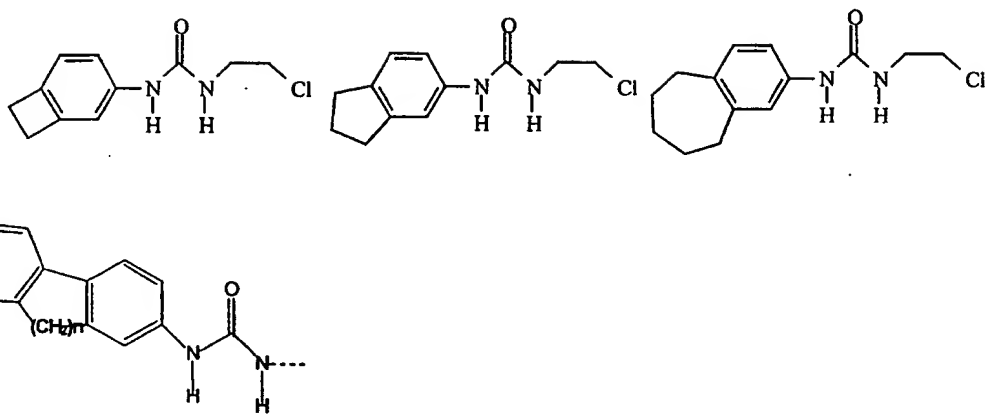
R_3 and R_4 are as defined in R_5 or halide, dihalide or trihalide (e.g. CF_3)
lower dialkyl (1 to 8 carbon atoms)
in R_3 and R_4, (the number of carbon atoms present is not necessarily identical ("asymetric molecules")) or
alicyclic groups of the following structures



wherein n = 2 to 8 carbon atoms,



R_3 and R_4 can also be polycyclic rings bearing not more than three rings such as dihydrophenanthrene, dihydroanthracene, anthracene, phenanthrene, fluorenyl, etc., examples:



wherein the rings other than the ring bearing the substituted 2-chloroethylamino moiety can be substituted by one or more groups as defined in R_5.

R_5 is H or
lower alkyl (1 to 7 carbon atoms) or
lower alkoxy or hydroxy alkyl , amino alkyl, thio alkyl (1 to 7 carbon atoms) or
S-lower alkyl
N-lower alkyl
N,N-dilower alkyl
lower cyanoalkyl (1 to 7 carbon atoms)
cycloalkyl (3 to 7 carbons atoms)
lower haloalkyls (Br, I, Cl, F) (1 to 7 carbon atoms)
lower sulfoxides (1 to 7 carbon atoms)

PREPARATION OF CEU DERIVATIVES

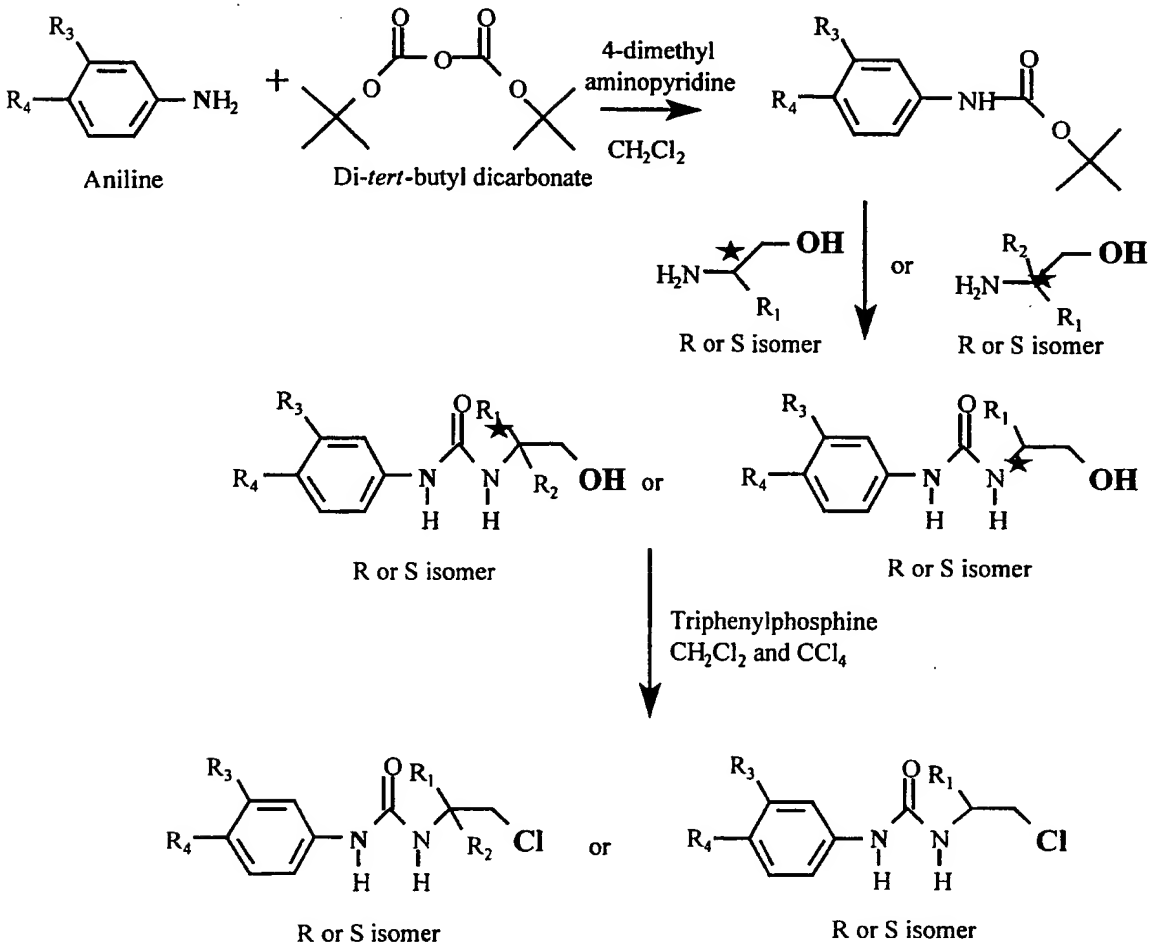
The compounds of the present invention are easily prepared in good yields without concomitant polymerization or decomposition. The compounds are also easily purified by usual techniques such as crystallization or liquid chromatography. Furthermore, the compounds exhibit an extended shelf life without decomposition in air.

The type and level of activity for a given dosage of each compound can be conventionally determined by routine experimentation using well-known pharmacological protocols.

The compounds of the present invention appear to kill cancer tumor cells by alkylation of their ß-tubulin on a specific cysteine residue (Cyst-239) and also by other mechanisms under investigation. The molecular structure of ß-tubulin has been highly conserved throughout evolution and is therefore present many mammalian cells. Consequently, the compounds of the invention are indicated for: wideranging anticancer agents, transdermic for pre-surgical treatment of melanomas and systemic for other cancers.

Prodrugs of the compounds of the present invention may also be easily prepared. As an example of prodrugs of the compounds of the present invention, the sulfone and sulfoxide derivatives of alkylthio substituents is immediately contemplated by skilled worker in this art. The sulfone and sulfoxide derivatives while not generally active will be activated once administered to a patient. The activation will occur when the prodrug is reduced to yield the corresponding alkylthio, an active compound.

The following synthesis flowsheet illustrates one route of preparation of CEU derivatives of the present invention.



It is important to note that the preparation of CEU derivatives of the present invention has led to the formation of R and S isomers which (in some cases) exhibit significant differences in cytotoxic activities (see Tables I and II below).

EXAMPLES

PREPARATION OF *N*-(4-ALKYLPHENYL)-*N'*-(1-ALKYL-2-HYDROXY)ETHYLUREAS

These compounds were prepared following the general synthetic route illustrated above.

To a stirred solution of di-*tert*-butyldicarbonate (3.9 mmol) and 4-dimethylaminopyridine (0.4 mmol) in anhydrous dichloromethane (20 mL) was added dropwise the relevant aniline (also 2-aminofluorenyl, 2-aminonaphthyl, etc. derivatives) (3.7 mmol). The reaction mixture was stirred for 30 min at room temperature and the required (R) or (S) aminoalcohol was added dropwise. The mixture was stirred overnight at room temperature. The solvent was evaporated under vacuum and the crude product was purified by flash chromatography on silica gel (dichloromethane/ethyl acetate, 20/80) to yield the hydroxyurea as a colorless solid.

HALOGENATION OF *N*-(4-ALKYLPHENYL)-*N'*-(1-ALKYL-2-HYDROXY)ETHYLUREAS INTO *N*-(4-ALKYLPHENYL)-*N'*-(1-ALKYL-2-CHLORO)ETHYLUREAS

A solution of the relevant hydroxyurea (2.4 mmol) and triphenylphosphine (3.7 mmol) in a mixture of dichloromethane and carbon tetrachloride (20 : 6) was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the crude product purified by flash chromatography on silica gel (ethylether/petroleum ether, 50/50) to give the chloroethylurea as a white solid.

Of import, the R_1 or/and R_2 substituted CEUs may also be prepared by several synthetic routes. One skilled in the art will quickly appreciate this.

EXAMPLE 1: EVALUATION OF CYTOTOXIC ACTIVITY

Compounds prepared in accordance with the method outlined above were synthesized and evaluated for cytotoxic activity. The molecular structure of each one of them was verified by IR, NMR and mass spectroscopy.

Table I below, provides the evaluation of the *in-vitro* cytotoxic activities of various compounds prepared in accordance with the synthesis illustrated above and in which R_3 and R_5 were H.

The conventional evaluation method proposed by the American National Cancer Institute was used. The method measures effectiveness of an anti-cancer drug based on IC_{50} which symbolizes the drug concentration in μM at which the drug achieves the inhibition of proliferation of a given line of cancer cells by a factor of one half when compared to the normal proliferation of the same line of cancer cells in the same growth media

Cytotoxicity Assay:

CEU were tested on several cell lines including human non-hormone-dependant breast cancer cells (MDA-MB-231), and mouse leukemia (L1210). MDA-MB-231. These cell lines were obtained from the American Type Culture Collection (Bethesda, MD, USA). Cytotoxicity of CEU derivatives was tested and compared to the effect of chlorambucil and carmustine.

Tumor cells were grown in RPMI-1640 medium supplemented with 10% fetal calf serum, 2 mM glutamine and 64 U/mL of gentamycin. Cells were routinely passaged at 90% confluence.

Five thousand cells (100 μl) were seeded in 96 well's plate and incubated for one day at 37°C under a humidified atmosphere, in presence of 5% CO_2. Subsequently, 100 μl of fresh medium containing CEU to obtain final concentrations ranging from 1- to 200 μM were added to the cultures. CEU were dissolved in dimethyl sulfoxide (DMSO; Aldrich Chemicals Company Inc., Milwaukee, WI) which is maintained at 0.5 % (v/v). Cells were incubated for four to five days in the presence of drugs.

Cell's survival was evaluated by colorimetric assay using MTT, according to a modification of the procedure reported by Carmichael and coll. [Carmichael J,

De Graff WG, Gazdar AF, Minna ID, Mitchell JB (1987) *Cancer Res 47*, 936-942]. Briefly, the culture media was replaced by 50 µl of a solution containing MTT (1.0 mg/ml in PBS: RPMI-1640, (1: 4)). The MTT is reduced by mitochondrial dehydrogenase to form MTT-formazan. After two hours of incubation at 37°C, the wells were washed with 200 µl of saline and 100 µL of DMSO containing 0.5% v/v of a glycine solution 0.1 M at pH 11 (NaOH) were added to dissolve the precipitate. The plates were then shaken for 15 minutes and the absorbance read at 570 nm with a Behring Elisa Procesor II (Behring, Marburg, Germany).

The evaluation was performed on two typical cancer cell lines namely, L1210 (mouse leukemia cells) and MDA-MB-231(human breast cancer cells). A comparison with conventional anti-cancer drugs chlorambucil and carmustine is provided to illustrate the effectiveness of the compounds of the present invention.

TABLE I *IN-VITRO* CYTOTOXIC ACTIVITY

IC_{50} L1210 (µM)	IC_{50} MDA-MB-231 (µM)	R_1	R_2	R_3	R_4
1.3	3.1	H	H	H	*sec*-butyl
2.0	4.5	R-methyl	H	H	*sec*-butyl
19.6	72.4	H	S-methyl H	H	*sec*-butyl
17	56	R-ethyl	H	H	*sec*-butyl
20.7	67	H	S-ethyl	H	*sec*-butyl
14	32	R and S-propyl	H	H	*sec*-butyl
15	Nd	Methyl	Methyl	H	*sec*-butyl
2.6	6.2	H	H	H	*tert*-butyl
2.3	6.1	R-methyl	H	H	*tert*-butyl
20	74	H	S-methyl	H	*tert*-butyl
19	55	R-ethyl	H	H	*tert*-butyl
16	67	H	S-ethyl	H	*tert*-butyl

IC_{50} L1210 (μM)	IC_{50} MDA-MB-231 (μM)	R_1	R_2	R_3	R_4
23	52	R and S-propyl	H	H	*tert*-butyl
>100	>100	Methyl	Methyl	H	*tert*-butyl
1.2	2.5	H	H	H	*iso*-propyl
0.5	1.7	R-methyl	H	H	*iso*-propyl
29.7	>100	H	S-methyl	H	*iso*-propyl
16	49	R-ethyl	H	H	*iso*-propyl
22	85	H	S-ethyl	H	*iso*-propyl
8.7	24	R and S-propyl	H	H	*iso*-propyl
80	>100	Methyl	Methyl	H	*iso*-propyl
4.5	6.8	Carmustine			
2.6	81	Chlorambucil			

The above experiments show that the R isomer on the R_1 group provided greater activity than the S isomer.

EXAMPLE 2

In a related set of experiments, the tert-butyl group of R4 was replaced with iodine to yield 4-iodoCEUs (bioisosteric form of the *tert*- butyl group). R_5 remained H. Table II below evaluates the cytotoxicity of such molecules and the effect of substitution on the 2-chloroethylamino moiety. During the experiments, IC_{50} was recorded against cancer cell lines L1210 and K562 (mouse leukemia cells).

TABLE II *IN-VITRO* CYTOTOXIC ACTIVITY

IC_{50} L1210 (μM)	IC_{50} K562 (μM)	R_1	R_2	R_3	R_4
5.4	3.8	H	H	H	I
1.6	1.1	R-methyl	H	H	I
10	7	H	S-methyl	H	I

This shows that the R isomer of the 4-iodoCEUs (bioisosteric form of the *tert*-butyl group) following a substitution on the 2-chloroethylamino moiety results in a very active drug.

EXAMPLE 3

In another related set of experiments wherein R_1 is H or CH_3, and R_2 is CH_3, the effect on substitutions on the phenyl ring were observed. It is theorized that theses substitutions assist in the positioning and selectivity of the compounds towards key intracellular proteins.

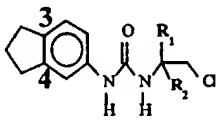
The results of *in-vitro* tests are reported in Table III below.

TABLE III *IN-VITRO* CYTOTOXIC ACTIVITY

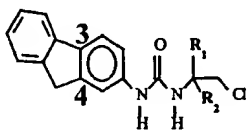
R_3	R_4	R_5	IC_{50} (μM) (MDA-MB-231)	IC_{50} (μM) L1210
H	Methyl	H	24.1	16.4
Methyl	H	H	60	27
Methyl	Methyl	H	7.2	3.8
Methyl	H	Methyl	20	8.8

From these observations, the R and S alkyl CEU deriving from 3,4 dimethylCEUs are particularly effective anti-cancer agents.

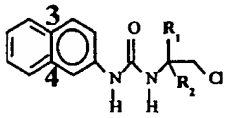
EXAMPLE 4



Ceu 1



Ceu 2



Ceu 3

In another experiment the following polycyclic molecules were prepared:

wherein R_1 is H or CH_3, and R_2 is CH_3.

In-vitro cytotoxic activities are reported in Table IV below.

TABLE IV *IN-VITRO* CYTOTOXIC ACTIVITY

DRUG	R_1	R_2	IC_{50} (μM) CHO	IC_{50} (μM) MDA-MB-231
CEU-1	H	H	9.9	10.3
CEU-1	R-methyl	H	9.8	9.5
CEU-1		S-methyl	78	>100
CEU-2	H	H	9.3	9.0
CEU-2	R-methyl	H	16.3	13
CEU-2	H	S-methyl	16.1	50
CEU-3	H	H	7.2	6.1
CEU-3	R-methyl	H	3.1	3.2
CEU-3	H	S-methyl	63	>100

These results show that the modification of the carbon 1' of CEU led to R and S isomers of CEU. R isomers are in most cases more cytotoxic than the unsubstituted CEU. Furthermore, R isomers are in most cases several fold more potent than the S isomers. This might be due to better specificity toward the protein(s) they alkylate.

EXAMPLE 5

The following compounds were successfully tested for cytotoxic acitivity.

R_1	R_2	R_5	IC_{50} (μM) CHO	IC_{50}(μM) HT-29	IC_{50}(μM) K562	IC_{50}(μM) MDA-MB-231
H	R-ethyl	tert-butyl	44	25	32.2	55
H	R-ethyl	iso-propyl	48	30	18	49
H	R-ethyl	sec-butyl	38	27	23	56
H	R-propyl	tert-butyl	60	27	21	52
H	R-propyl	iso-propyl	21.3	17	6	24
H	R-propyl	sec-butyl	29	16.4	11	32

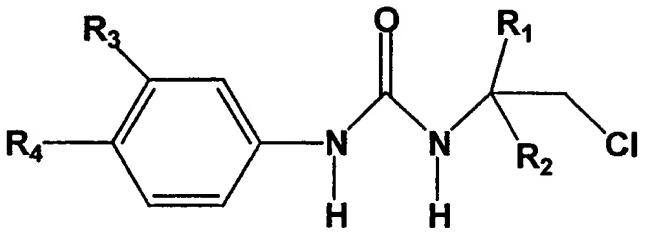
CHO = Chinese Hamster Ovary

MDA-MB-231 Hormone-independant breast cancer

HT-29 human colon carcinoma

K562 human leukemia

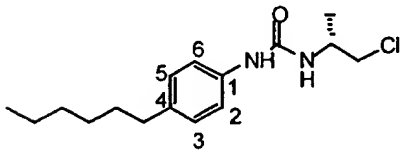
EXAMPLES 6-15



Based on the formula of the compounds of the present invention as shown above, specific molecules were synthesized and later tested for citotoxic activity.

EXAMPLE 6

R_1	R_2	R_3	R_4
H	Methyl (S configuration)	H	n-hexyl



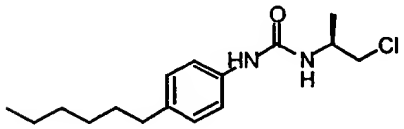
Flash chromatography : ether : petrol ether = 1 :1

R_f = 0.31 (ether : petrol ether = 1 : 1)

^{1}H-NMR ($CDCl_3$) : 7.17 (d, 2H, H-C2 and H-C6, J = 8.4 Hz), 7.11 (d, 2H, H-C3 and H-C5, J = 8.4 Hz), 4.27 (m, 1H, $CH(CH_3)CH_2Cl$), 3.72 (dd, 1H, CH_2Cl, J = 4.3 and J = 11.0 Hz), 3.57 (dd, 1H, CH_2Cl, J = 3.4 and J = 11.0 Hz), 2.55 (t, 2H, $CH_3(CH_2)_4CH_2$), 1.53 (m, 2H, $CH_3(CH_2)_3CH_2CH_2$), 1.23 (d, 3H, $CH(CH_3)CH_2Cl$, J = 6.9 Hz), 1.18-1.43 (m, 6H, $CH_3(CH_2)_3CH_2CH_2$), 0.87 (t, 3H, $CH_3(CH_2)_5$).

EXAMPLE 7

R_1	R_2	R_3	R_4
H	Methyl(Rconfiguration)	H	n-hexyl



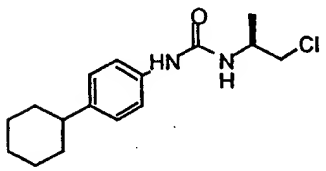
Flash chromatography : ether : petrol ether = 2 :3

R_f = 0.29 (ether : petrol ether = 2 : 3)

^{1}H-NMR ($CDCl_3$) : 7.16 (d, 2H, H-C2 and H-C6, J = 8.5 Hz), 7.07 (d, 2H, H-C3 and H-C5, J = 8.5 Hz), 5.33 (br s, 1H, NH), 4.23 (m, 1H, $CH(CH_3)CH_2Cl$), 3.65 (dd, 1H, CH_2Cl, J = 4.5 and J = 11.0 Hz), 3.53 (dd, 1H, CH_2Cl, J = 3.5 and J = 11.0 Hz), 2.52 (t, 2H, $CH_3(CH_2)_4CH_2$, J = 7.5 Hz), 1.50-1.60 (m, 2H, $CH_3(CH_2)_3CH_2CH_2$), 1.28 (m, 6H, $CH_3(CH_2)_3CH_2CH_2$), 1.19 (d, 3H, $CH(CH_3)CH_2Cl$, J = 6.7 Hz), 0.87 (t, 3H, $CH_3(CH_2)_5$, J = 6.5 Hz).

EXAMPLE 8

R_1	R_2	R_3	R_4
H	Methyl (R configuration)	H	Cyclohexyl



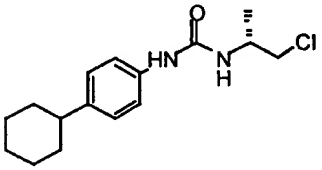
Flash chromatography : ether : petrol ether = 1 :1

^{1}H-NMR ($CDCl_3$) : 7.16 (d, 2H, H-C2 and H-C6, J = 8.4 Hz), 7.11 (d, 2H, H-C3 and H-C5, J = 8.4 Hz), 4.24 (m, 1H, $CH(CH_3)CH_2Cl$), 3.66 (dd, 1H, CH_2Cl, J = 4.2 and J = 11.0 Hz), 3.54 (dd, 1H, CH_2Cl, J = 3.4 and J = 11.0 Hz), 2.43 (m,

1H, CH-Ph), 1.70-1.90 (m, 6H, H-cyclohexyl), 1.35-1.45 (m, 4H, H-cyclohexyl), 1.20 (d, 3H, $CH(CH_3)CH_2Cl$, J = 6.7 Hz).

EXAMPLE 9

R_1	R_2	R_3	R_4
H	Methyl (S configuration)	H	cyclohexyl



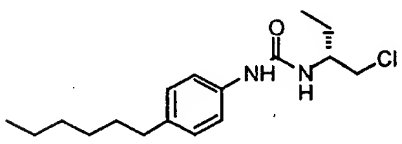
Flash chromatography : ether : petrol ether = 1 :1

R_f = 0.24 (ether : petrol ether = 1 : 1)

^{1}H-NMR ($CDCl_3$) : 7.18 (d, 2H, H-C2 and H-C6, J = 8.7 Hz), 7.14 (d, 2H, H-C3 and H-C5, J = 8.7 Hz), 4.27 (m, 1H, $CH(CH_3)CH_2Cl$), 3.71 (dd, 1H, CH_2Cl, J = 4.4 and J = 11.0 Hz), 3.56 (dd, 1H, CH_2Cl, J = 3.2 and J = 11.0 Hz), 2.45 (m, 1H, CH-Ph), 1.70-1.85 (m, 6H, H-cyclohexyl), 1.36 (m, 4H, H-cyclohexyl), 1.23 (d, 3H, $CH(CH_3)CH_2Cl$, J = 6.8 Hz).

EXAMPLE 10

R_1	R_2	R_3	R_4
H	-ethyl (R configuration)	H	n-hexyl



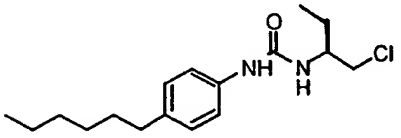
Flash chromatography : ether : petrol ether = 10 :11

R_f = 0.38 (ether : petrol ether = 1 : 1)

^{1}H-NMR ($CDCl_3$) : 7.17 (d, 2H, H-C2 and H-C6, J = 8.4 Hz), 7.08 (d, 2H, H-C3 and H-C5, J = 8.4 Hz), 5.24 (br s, 1H, NH), 4.02 (m, 1H, $CH(CH_2CH_3)CH_2Cl$), 3.69 (dd, 1H, CH_2Cl, J = 4.0 and 11.0 Hz), 3.60 (dd, 1H, CH_2Cl, J = 3.3 and 11.0 Hz), 2.53 (t, 2H, CH_2Ph, J = 7.8 Hz), 1.56 (m, 4H, $CH_3(CH_2)_3CH_2CH_2$ and $CH(CH_2CH_3)CH_2Cl$), 1.28 (m, 6H, $CH_3(CH_2)_3CH_2CH_2$), 0.89 (2t, 6H, $CH_3(CH_2)_5$ and $CH(CH_2CH_3)CH_2Cl$, J = 6.5 and 7.4 Hz).

EXAMPLE 11

R_1	R_2	R_3	R_4
H	-ethyl (R configuration)	H	n-hexyl



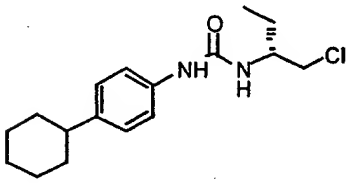
Flash chromatography : ether : petrol ether = 35 :65

R_f = 0.28 (ether : petrol ether = 2 : 3)

^{1}H-NMR ($CDCl_3$) : 7.16 (d, 2H, H-C2 and H-C6, J = 8.2 Hz), 7.06 (d, 2H, H-C3 and H-C5, J = 8.2 Hz), 5.41 (br s, 1H, NH), 4.02 (m, 1H, $CH(CH_2CH_3)CH_2Cl$), 3.67 (dd, 1H, CH_2Cl, J = 4.2 and 11.0 Hz), 3.58 (dd, 1H, CH_2Cl, J = 3.5 and 11.0 Hz), 2.52 (t, 2H, CH_2Ph, J = 7.7 Hz), 1.55 (m, 4H, $CH_3(CH_2)_3CH_2CH_2$ and $CH(CH_2CH_3)CH_2Cl$), 1.28 (m, 6H, $CH_3(CH_2)_3CH_2CH_2$), 0.89 (2t, 6H, $CH_3(CH_2)_5$ and $CH(CH_2CH_3)CH_2Cl$, J = 6.6 and 7.5 Hz).

EXAMPLE 12

R_1	R_2	R_3	R_4
H	Ethyl (S configuration)	H	cyclohexyl



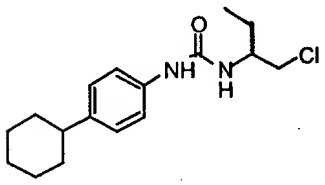
Flash chromatography : ether : petrol ether = 10 :11

R_f = 0.38 (ether : petrol ether = 1 : 1)

^{1}H-NMR ($CDCl_3$) : 7.18 (d, 2H, H-C2 and H-C6, J = 8.7 Hz), 7.14 (d, 2H, H-C3 and H-C5, J = 8.7 Hz), 4.04 (m, 1H, $CH(CH_3)CH_2Cl$), 3.73 (dd, 1H, CH_2Cl, J = 4.0 and J = 11.2 Hz), 3.63 (dd, 1H, CH_2Cl, J = 3.2 and J = 11.2 Hz), 2.46 (m, 1H, CH-Ph), 1.70-1.85 (m, 4H, H-cyclohexyl), 1.58 (m, 2H, $CH(CH_2CH_3)CH_2Cl$), 1.18-1.45 (m, 6H, H-cyclohexyl), 0.93 (t, 3H, $CH(CH_2CH_3)CH_2Cl$, J = 7.4 Hz).

EXAMPLE 13

R_1	R_2	R_3	R_4
H	Ethyl (R configuration)	H	cyclohexyl



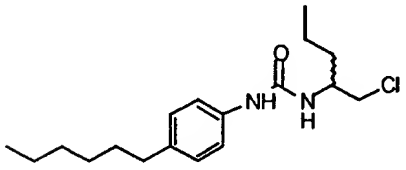
Flash chromatography : ether : petrol ether = 1 :1

R_f = 0.35 (ether : petrol ether = 1 : 1)

^{1}H-NMR ($CDCl_3$) : 7.18 (d, 2H, H-C2 and C6, J = 8.5 Hz), 7.13 (d, 2H, H-C3 and H-C5, J = 8.5 Hz), 4.03 (m, 1H, $CH(CH_3)CH_2Cl$), 3.72 (dd, 1H, CH_2Cl, J = 3.9 and J = 11.1 Hz), 3.64 (dd, 1H, CH_2Cl, J = 3.4 and J = 11.1 Hz), 2.45 (m, 1H, CH-Ph), 1.65-1.95 (m, 4H, H-cyclohexyl), 1.56 (m, 2H, $CH(CH_2CH_3)CH_2Cl$), 1.20-1.40 (m, 6H, H-cyclohexyl), 0.93 (t, 3H, $CH(CH_2CH_3)CH_2Cl$, J = 7.4 Hz).

EXAMPLE 14

R_1	R_2	R_3	R_4
H	Propyl (mixture of R and S isomers)	H	n-hexyl



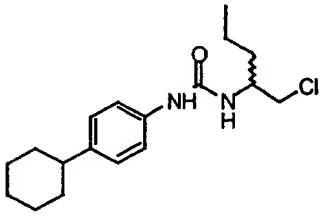
Flash chromatography : ether : petrol ether = 2 :3

R_f = 0.31 (ether : petrol ether = 2 : 3)

^{1}H-NMR ($CDCl_3$) : 7.17 (d, 2H, H-C2 et C6, J = 8.2 Hz), 7.04 (d, 2H, H-C3 et C5, J = 8.2 Hz), 4.05 (m, 1H, $CH(CH_2CH_2CH_3)CH_2Cl$), 3.64 (dd, 1H, CH_2Cl, J = 4.3 et J = 11 Hz), 3.54 (dd, 1H, CH_2Cl, J = 3.7 et J = 11 Hz), 2.51 (t, 2H, $CH_3(CH_2)_4CH_2$, J = 7.7 Hz), 1.25-1.60 (m, 12H, $CH_3(CH_2)_4CH_2$ and $CH(CH_2CH_2CH_3)CH_2Cl$), 0.88 (t, 3H, $CH(CH_2CH_2CH_3)CH_2Cl$, J = 7.2 Hz).

EXAMPLE 15

R_1	R_2	R_3	R_4
H	Propyl (mixture of R and S isomers)	H	cyclohexyl



^{1}H-NMR ($CDCl_3$) : 7.18 (d, 2H, H-C2 et C6, J = 8.7 Hz), 7.13 (d, 2H, H-C3 et C5, J = 8.7 Hz), 4.13 (m, 1H, $CH(CH_2CH_2CH_3)CH_2Cl$), 3.73 (dd, 1H, CH_2Cl, J = 4.1 et J = 11.1 Hz), 3.59 (dd, 1H, CH_2Cl, J = 3.5 et J = 11.1 Hz), 2.45 (m, 1H, CH-Ph), 1.20-2.00 (m, 14H, CH_2-cyclohexyl et $CH(CH_2CH_2CH_3)CH_2Cl$), 0.91 (t, 3H, $CH(CH_2CH_2CH_3)CH_2Cl$, J = 7.1 Hz).

EXAMPLE 16: EVALUATION OF CYTOTOXYCITY ACTIVITY:

Cell culture. Tumor cell lines (B16-F0, Caco-2, DU-145, HT-29, MDA-MB-231 and other cell lines described so far in the patent application) were obtained from the American Type Culture Collection (ATCC HTB-26; Bethesda, MD). Cells were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum (Hyclone, Road Logan, Utah) and were cultured in a humidified atmosphere at 37 °C in 5% CO_2.

Drugs: All drugs were dissolved in DMSO and the final concentration of DMSO in the culture medium was maintained at 0.5 % (v/v).

Cytotoxiciy assays. At day-1, tumor cells in suspension in 100 μl were plated in microtiter plates (96 wells). On day-0, tumor cells were treated by addition of escalating concentrations of the drug (100μl solution). On that day, the number of living cells was determined in wells that were untreated. This was performed in order to be able to evaluate the toxic concentration of the drug needed to kill

50% of the cellular population present at the beginning of the experiments. This value is represented by C_{50} in the table. At day-3, the number of living cells is determined using either MTT or resazurin assays. Growth inhibition activity of these compounds was expressed as the concentration of CEU inhibiting cell growth by 50% G50 in the following table

The MTT assay was as described above in Example 1. The Resazurin assay was performed as follows:

Aspirate the supernatant (cell suspension: centrifuge first)
Add 100 µL NaCl 0.9% (saline)
Aspirate the supernatant (cell suspension: centrifuge first)
Add 50 µL RZ (resazurin 125 µg/ml/PBS : RPMI without FBS ; 1 : 4)
Incubate at 37°C
Collect fluorescence data at different time.

FILTER	EM	EM
CENTER	590	590

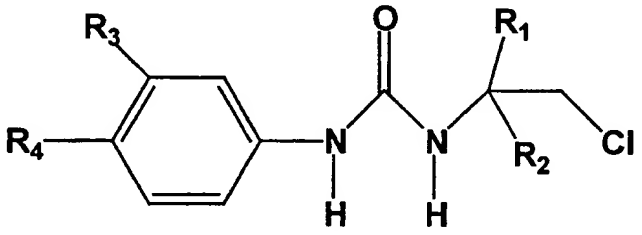
TABLE V *IN-VITRO* CYTOTOXIC ACTIVITY

Cell line	R_1	R_2	R_3	R_4	C_{50} (µM)	G_{50} (µM)	C_{50}/G_{50}
HT-29	H	Methyl (R isomer	H	n-hexyl	12.8	5.1	2.51
DU-145	idem	idem	Idem	Idem	11.8	6.3	1.86
MDA-MB-231	idem	idem	Idem	Idem	31.9	11.7	2.72
Caco-2	idem	idem	Idem	Idem	21.1	12.6	1.68
B16-F0	idem	idem	idem	Idem	18.2	16.3	1.12
DU-145	H	Methyl (S isomer)	H	n-hexyl	39.5	18.9	2.09
B16-F0	idem	idem	idem	Idem	31.3	26.3	1.19
MDA-MB-231	idem	idem	idem	Idem	43.3	31.5	1.37
HT-29	idem	idem	idem	Idem	44.5	32.3	1.38
Caco-2	idem	idem	idem	Idem	44.2	35.8	1.23
HT-29	H	propyl (racemic	H	n-hexyl	20.3	10.7	1.90

Cell line	R_1	R_2	R_3	R_4	C_{50} (μM)	G_{50} (μM)	C_{50}/G_{50}
		mixture)					
DU-145	idem	idem	idem	Idem	19.6	10.9	1.80
Caco-2	idem	idem	idem	Idem	21.1	12.7	1.34
B16-F0	idem	idem	idem	Idem	21.3	15.8	1.71
MDA-MB-231	idem	idem	idem	Idem	32.3	18.9	1.71
DU-145	H	ethyl (S isomer)	H	n-hexyl	27.2	7.4	3.68
Caco-2	idem	idem	idem	Idem	13.7	10.2	1.35
MDA-MB-231	idem	idem	idem	Idem	40.6	18	
B16-F0	idem	idem	idem	Idem	24.9	18.8	1.33
HT-29	idem	idem	idem	Idem	36.8	20.8	1.77
DU-145	H	ethyl (R isomer)	H	n-hexyl	15.8	4.6	3.46
Caco-2	idem	idem	idem	idem	10.9	7.5	1.45
HT-29	idem	idem	idem	idem	20.8	13.1	1.58
B16-F0	idem	idem	idem	idem	18.3	14.1	1.29
MDA-MB-231	idem	idem	idem	idem	30.1	15.1	1.99
DU-145	H	methyl (S isomer)	H	cyclohexyl	27.6	7.8	3.52
Caco-2	idem	idem	idem	idem	14.7	8.6	1.70
B16-Fo	idem	idem	idem	idem	17.4	15.4	1.13
HT-29	idem	idem	idem	idem	28.1	19	1.48
MDA-MB-231	idem	idem	idem	idem	42.9	27.5	1.56
DU-145	H	methyl (R isomer)	H	cyclohexyl	25.2	8.6	2.94
Caco-2	idem	idem	idem	idem	20.3	15.4	1.32
HT-29	idem	idem	idem	idem	23.9	17.1	1.40
B16-F0	idem	idem	idem	idem	22.1	21.8	1.01
MDA-MB-231	idem	idem	idem	idem	42.3	27.6	1.53
DU-145	H	ethyl (S isomer)	H	cyclohexyl	22.2	7.3	3.04
Caco-2	idem	idem	idem	idem	17.7	10	1.77
HT-29	idem	idem	idem	idem	22.8	13.6	1.68
B16-F0	idem	idem	idem	idem	21.5	17.3	1.24
MDA-MB-231	idem	idem	idem	idem	40.3	19.6	2.05

Cell line	R_1	R_2	R_3	R_4	C_{50} (μM)	G_{50} (μM)	C_{50}/G_{50}
DU-145	H	ethyl (R isomer)	H	cyclohexyl	16.2	6.9	2.35
HT-29	idem	idem	idem	idem	16.3	9.8	2.35
Caco-2	idem	idem	idem	idem	15.6	9.9	1.57
B16-F0	idem	idem	idem	idem	17.7	15.5	1.14
MDA-MB-231	idem	idem	idem	idem	32.5	16.3	1.99

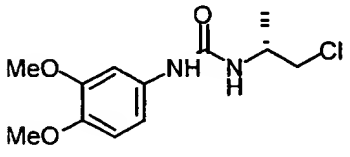
EXAMPLES 17-29



Based on the formula of the compounds of the present invention as shown above, specific molecules were synthesized and later tested for citotoxic activity.

EXAMPLE 17

R1	R2	R3	R4
H	Methyl (R-isomer)	Methoxy	Methoxy



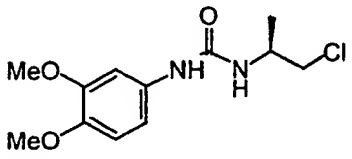
Flash chromatography : 9 / 1 : ether / petrol ether

R_f = 0.31 (100% ether)

^{1}H-NMR ($CDCl_3$) : 6.95 (d, 1H, H-C2, J = 2.2 Hz), 6.72 (d, 1H, H-C5, J = 8.4 Hz), 6.64 (dd, 1H, H-C6, J = 2.0 and J = 8.4 Hz), 4.21 (m, 1H, C**H**(CH_3)CH_2Cl), 3.78 (s, 6H, 2 OCH_3), 3.67 (dd, 1H, C**H**$_2$Cl, J = 4.1 and J = 10.9 Hz), 3.50 (dd, 1H, C**H**$_2$Cl, J = 3.3 and J = 10.9 Hz), 1.17 (t, 3H, CH(C**H**$_3$)CH_2Cl, J = 6.7 Hz).

EXAMPLE 18

R1	R2	R3	R4
H	Methyl (S-isomer)	Methoxy	Methoxy



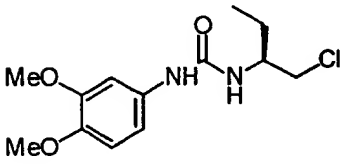
Flash chromatography : 9 / 1 : ether / petrol ether

R_f = 0.33 (100% ether)

^{1}H-NMR ($CDCl_3$) : 6.96 (d, 1H, H-C2, J = 2 Hz), 6.70 (d, 1H, H-C5, J = 8.5 Hz), 6.63 (d, 1H, H-C6, J = 8.5 Hz), 4.20 (m, 1H, C**H**(CH_3)CH_2Cl), 3.76 et 3.78 (2s, 6H, 2 OCH_3), 3.65 (dd, 1H, C**H**$_2$Cl, J = 4.2 and J = 11.0 Hz), 3.49 (dd, 1H, C**H**$_2$Cl, J = 3.4 and J = 11.0 Hz), 1.16 (t, 3H, CH(C**H**$_3$)CH_2Cl, J = 6.8 Hz).

EXAMPLE 19

R1	R2	R3	R4
H	Ethyl (S-isomer)	Methoxy	Methoxy



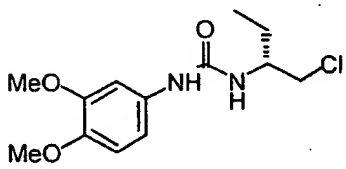
Flash chromatography :7 / 3 : ether / petrol ether

R_f = 0.17 (7 / 3 : ether / petrol ether)

^{1}H-NMR ($CDCl_3$): 6. 99 (d, 1H, H-C2, J = 2.3 Hz), 6.80 (d, 1H, H-C5, J = 8.4 Hz), 6.72 (d, 1H, H-C6, J = 8.4 Hz), 4.04 (m, 1H, $CH(CH_2CH_3)CH_2Cl$), 3.85 (s, 6H, 2 OCH_3), 3.75 (dd, 1H, CH_2Cl, J = 3.9 and J = 11.2 Hz), 3.63 (dd, 1H, CH_2Cl, J = 3.3 and J = 11.2 Hz), 1.57 (m, 2H, $CH(CH_2CH_3)CH_2Cl$), 0.93 (t, 3H, $CH(CH_2CH_3)CH_2Cl$, J = 7.5 Hz).

EXAMPLE 20

R1	R2	R3	R4
H	Ethyl (R-isomer)	Methoxy	Methoxy



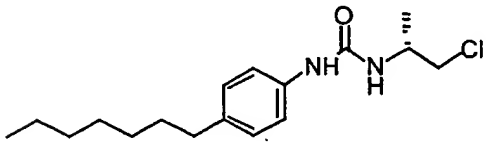
Flash chromatography :7 / 3 : ether / petrol ether

R_f = 0.17 (7 / 3 : ether / petrol ether)

^{1}H-NMR ($CDCl_3$): 7.02 (d, 1H, H-C2, J = 2.2 Hz), 6.77 (d, 1H, H-C5, J = 8.7 Hz), 6.70 (dd, 1H, H -C6, J = 2.2 and J = 8.7 Hz), 4.03 (m, 1H, $CH(CH_2CH_3)CH_2Cl$), 3.83 (s, 6H, 2 OCH_3), 3.73 (dd, 1H, CH_2Cl, J = 4.0 and J = 11.2 Hz), 3.61 (dd, 1H, CH_2Cl, J = 3.2 and J = 11.2 Hz), 1.56 (m, 2H, $CH(CH_2CH_3)CH_2Cl$), 0.92 (t, 3H, $CH(CH_2CH_3)CH_2Cl$, J = 7.4 Hz).

EXAMPLE 21

R1	R2	R3	R4
H	Methyl (R-isomer)	H	n-heptyl



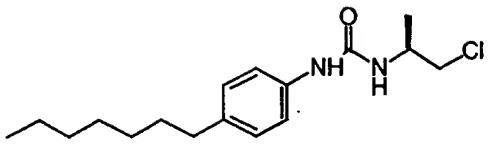
Flash chromatography : 35 / 65 : ether / petrol ether

R_f = 0.16 (2 / 3 : ether / petrol ether)

^{1}H-NMR ($CDCl_3$): 7.15 (d, 2H, H-C2 and H-C6, J = 8.4 Hz), 7.07 (d, 2H, H-C3 and H-C5, J = 8.4 Hz), 4.25 (m, 1H, $CH(CH_3)CH_2Cl$), 3.65 (dd, 1H, $CH(CH_3)CH_2Cl$, J = 4.5 and J = 11.0 Hz), 3.53 (dd, 1H, $CH(CH_3)CH_2Cl$, J = 3.6 and J = 11.0 Hz), 2.53 (t, 2H, $CH_3(CH_2)_5CH_2$, J = 7.8 Hz), 1.55 (m, 2H, $CH_3(CH_2)_4CH_2CH_2$), 1.28 (m, 8H, $CH_3(CH_2)_4CH_2CH_2$), 1.20 (d, 3H, $CH(CH_3)CH_2Cl$, J = 6.7 Hz), 0.87 (t, 3H, $CH_3(CH_2)_6$, J = 6.8 Hz).

EXAMPLE 22

R1	R2	R3	R4
H	Methyl (S-isomer)	H	n-heptyl



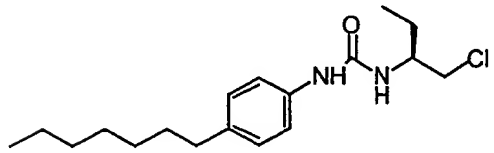
Flash chromatography : 4 / 5 / 1 : CH_2Cl_2 / petrol ether / ether

R_f = 0.23 (2 / 3 : ether / petrol ether)

^{1}H-NMR ($CDCl_3$) : 7.16 (d, 2H, H-C2 and H-C6, J = 8.3 Hz), 7.07 (d, 2H, H-C3 and H-C5, J = 8.3 Hz), 4.23 (m, 1H, C**H**(CH_3)CH_2Cl), 3.65 (dd, 1H, CH(CH_3)C**H**$_2$Cl, J = 4.5 and J = 11.0 Hz), 3.53 (dd, 1H, CH(CH_3)C**H**$_2$Cl, J = 3.5 and J = 11.0 Hz), 2.52 (t, 2H, $CH_3(CH_2)_5CH_2$, J = 7.7 Hz), 1.55 (m, 2H, $CH_3(CH_2)_4CH_2CH_2$), 1.28 (m, 8H, $CH_3(CH_2)_4CH_2CH_2$), 1.19 (d, 3H, CH(CH_3)CH_2Cl, J = 6.6 Hz), 0.87 (t, 3H, $CH_3(CH_2)_6$, J = 6.6 Hz).

EXAMPLE 23

R1	R2	R3	R4
H	Ethyl (S-isomer)	H	n-heptyl



Flash chromatography : 4 / 5 / 1 : CH_2Cl_2 / petrol ether / ether

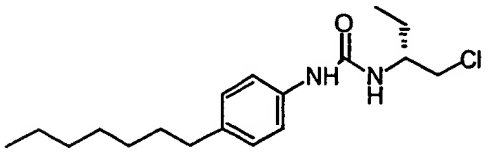
R_f = 0.31 (2 / 3 : ether / petrol ether)

^{1}H-NMR ($CDCl_3$) : 7.17 (d, 2H, H-C2 and H-C6, J = 8.2 Hz), 7.09 (d, 2H, H-C3 and H-C5, J = 8.2 Hz), 4.03 (m, 1H, C**H**(CH_2CH_3)CH_2Cl), 3.70 (dd, 1H, CH(CH_2CH_3)C**H**$_2$Cl, J = 3.7 and J = 11.0 Hz), 3.61 (dd, 1H, CH(CH_2CH_3)C**H**$_2$Cl, J = 3.2 and J = 11.0 Hz), 2.53 (t, 2H, $CH_3(CH_2)_5CH_2$, J = 7.7 Hz), 1.57 (m, 4H, $CH_3(CH_2)_4CH_2CH_2$ and CH(C**H**$_2$$CH_3$)$CH_2Cl$), 1.27 (m, 8H, $CH_3(CH_2)_4CH_2CH_2$),

0.92 and 0.87 (2t, 6H, $CH_3(CH_2)_6$ and $CH(CH_2CH_3)CH_2Cl$, J = 7.6 and J = 7.0 Hz).

EXAMPLE 24

R1	R2	R3	R4
H	Ethyl (R-isomer)	H	n-heptyl



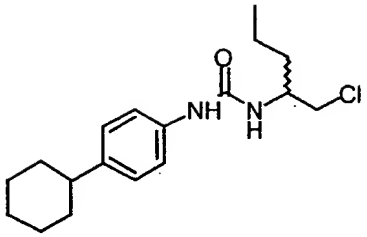
Flash chromatography : 4 / 5 / 1 : CH_2Cl_2 / petrol ether / ether

R_f = 0.31 (2 / 3 : ether / petrol ether)

^{1}H-NMR ($CDCl_3$) : 7.16 (d, 2H, H-C2 and H-C6 J = 8.5 Hz), 7.06 (d, 2H, H-C3 and H-C5, J = 8.5 Hz), 4.00 (m, 1H, $CH(CH_2CH_3)CH_2Cl$), 3.67 (dd, 1H, $CH(CH_2CH_3)CH_2Cl$, J = 4.2 and J = 11.1 Hz), 3.58 (dd, 1H, $CH(CH_2CH_3)CH_2Cl$, J = 3.5 and J = 11.1 Hz), 2.53 (t, 2H, $CH_3(CH_2)_5CH_2$, J = 7.7 Hz), 1.54 (m, 4H, $CH_3(CH_2)_4CH_2CH_2$ and $CH(CH_2CH_3)CH_2Cl$), 1.28 (m, 8H, $CH_3(CH_2)_4CH_2CH_2$), 0.91 and 0.87 (2t, 6H, $CH_3(CH_2)_6$ and $CH(CH_2CH_3)CH_2Cl$, J = 7.4 and J = 7.1 Hz).

EXAMPLE 25

R1	R2	R3	R4
H	Propyl (racemic mixture)	H	cyclohexyl



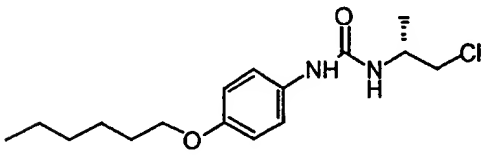
Flash chromatography : 2 / 3 : ether / petrol ether

R_f = 0.31 (2 / 3 : ether / petrol ether)

^{1}H-NMR ($CDCl_3$) : 7.16 (d, 2H, H-C2 and H-C6, J = 8.6 Hz), 7.08 (d, 2H, H-C3 and H-C5, J = 8.6 Hz), 4.08 (m, 1H, $CH(CH_2CH_2CH_3)CH_2Cl$), 3.66 (dd, 1H, CH_2Cl, J = 4.2 and J = 11.0 Hz), 3.55 (dd, 1H, CH_2Cl, J = 3.6 and J = 11.0 Hz), 2.42 (m, 1H, CH-Ph), 1.70-1.82 (m, 6H, $CH(CH_2CH_2CH_3)CH_2Cl$ and H-cyclohexyl), 1.20-1.60 (m, 8H, $CH(CH_2CH_2CH_3)CH_2Cl$ and H-cyclohexyl), 0.88 (t, 3H, $CH(CH_2CH_2CH_3)CH_2Cl$, J = 7.2 Hz).

EXAMPLE 26

R1	R2	R3	R4
H	Methyl (R-isomer)	H	n-hexyloxy



Flash chromatography : 1 / 1 : ether / petrol ether

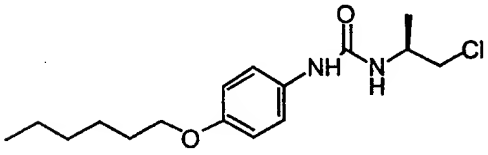
R_f = 0.16 (1 / 1 : ether / petrol ether)

^{1}H-NMR ($CDCl_3$) : 7.16 (d, 2H, H-C2 and H-C6, J = 8.7 Hz), 6.85 (d, 2H, H-C3 and H-C5, J = 8.7 Hz), 4.26 (m, 1H, $CH(CH_3)CH_2Cl$), 3.92 (t, 2H, $CH_3(CH_2)_4CH_2O$, J = 6.6 Hz), 3.72 (dd, 1H, $CH(CH_3)CH_2Cl$, J = 4.3 and J = 11.0 Hz), 3.55 (dd, 1H, $CH(CH_3)CH_2Cl$, J = 3.5 and J = 11.0 Hz), 1.76 (m, 2H,

$CH_3(CH_2)_3CH_2CH_2O$), 1.24-1.50 (m, 6H, $CH_3(CH_2)_3CH_2CH_2O$), 1.21 (d, 3H, $CH(CH_3)CH_2Cl$, J = 6.7 Hz), 0.90 (t, 3H, $CH_3(CH_2)_5O$, J = 6.9 Hz).

EXAMPLE 27

R1	R2	R3	R4
H	Methyl (S-isomer)	H	n-hexyloxy



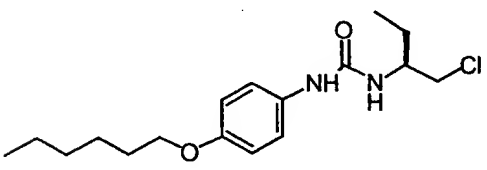
Flash chromatography : 55 / 35 / 10 : CH_2Cl_2 / petrol ether / ether

R_f = 0.16 (1 / 1 : ether / petrol ether)

^{1}H-NMR ($CDCl_3$) : 7.13 (d, 2H, H-C2 and H-C6, J = 7.7 Hz), 6.79 (d, 2H, H-C3 and H-C5, J = 7.7 Hz), 4.21 (m, 1H, $CH(CH_3)CH_2Cl$), 3.87 (t, 2H, $CH_3(CH_2)_4CH_2O$, J = 6.5 Hz), 3.64 (dd, 1H, $CH(CH_3)CH_2Cl$, J = 4.5 and J = 11.0 Hz), 3.52 (dd, 1H, $CH(CH_3)CH_2Cl$, J = 3.5 and J = 11.0 Hz), 1.74 (m, 2H, $CH_3(CH_2)_3CH_2CH_2O$), 1.24-1.45 (m, 6H, $CH_3(CH_2)_3CH_2CH_2O$), 1.18 (d, 3H, $CH(CH_3)CH_2Cl$, J = 6.6 Hz), 0.89 (m, 3H, $CH_3(CH_2)_5O$).

EXAMPLE 28

R1	R2	R3	R4
H	Ethyl (S-isomer)	H	n-hexyloxy



Flash chromatography : 55 / 35 / 10 : CH_2Cl_2 / petrol ether / ether

R_f = 0.26 (1 / 1 : ether / petrol ether)

^{1}H-NMR ($CDCl_3$) : 7.16 (d, 2H, H-C2 and C6, J = 8.8 Hz), 6.82 (d, 2H, H-C3 and C5, J = 8.8 Hz), 4.01 (m, 1H, $CH(CH_3)CH_2Cl$), 3.90 (t, 2H, $CH_3(CH_2)_4CH_2O$, J = 6.6 Hz), 3.70 (dd, 1H, $CH(CH_2CH_3)CH_2Cl$, J = 4.0 and J = 11.2 Hz), 3.60 (dd, 1H, $CH(CH_2CH_3)CH_2Cl$, J = 3.3 and J = 11.2 Hz), 1.75 (m, 2H, $CH_3(CH_2)_3CH_2CH_2O$), 1.20-1.70 (m, 8H, $CH_3(CH_2)_3CH_2CH_2O$) and $CH(CH_2CH_3)CH_2Cl$), 0.90 (2t, 6H, $CH_3(CH_2)_5O$ and $CH(CH_2CH_3)CH_2Cl$, J = 7.4 and J = 6.5 Hz).

EXAMPLE 29: EVALUATION OF CYTOTOXYCITY ACTIVITY:

Cell culture. Tumor cell lines (B16-F0, Caco-2, DU-145, HT-29, MDA-MB-231 and other cell lines described so far in the patent application) were obtained from the American Type Culture Collection (ATCC HTB-26; Bethesda, MD). Cells were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum (Hyclone, Road Logan, Utah) and were cultured in a humidified atmosphere at 37 °C in 5% CO_2.

Drugs: All drugs were dissolved in DMSO and the final concentration of DMSO in the culture medium was maintained at 0.5 % (v/v).

Cytotoxiciy assays. At day-1, tumor cells in suspension in 100 μl were plated in microtiter plates (96 wells). On day-0, tumor cells were treated by addition of escalating concentrations of the drug (100μl solution). On that day, the number of living cells was determined in wells that were untreated. The number of living cells is determined using either MTT or resazurin assays. Growth inhibition activity of these compounds was expressed as the concentration of CEU inhibiting cell growth by 50% G_{50} in the following table

The MTT assay was as described above in Example 1. The Resazurin assay was performed as follows:

Aspirate the supernatant (cell suspension: centrifuge first)

Add 100 µL NaCl 0.9% (saline)

Aspirate the supernatant (cell suspension: centrifuge first)

Add 50 µL RZ (resazurin 125 µg/ml/PBS : RPMI without FBS ; 1 : 4)

Incubate at 37°C

Collect fluorescence data at different time.

FILTER	EM	EM
CENTER	590	590

TABLE VI *IN-VITRO* CYTOTOXIC ACTIVITY

Cell line	R1	R2	R3	R4	G50 (µM)
B16-F0	H	Ethyl (R-isomer)	H	n-Heptyl	3,74
Caco-2	H	Ethyl (R-isomer)	H	n-Heptyl	4,85
CHO	H	Ethyl (R-isomer)	H	n-Heptyl	3,14
DU-145	H	Ethyl (R-isomer)	H	n-Heptyl	4,02
HT-29	H	Ethyl (R-isomer)	H	n-Heptyl	2,94
K562	H	Ethyl (R-isomer)	H	n-Heptyl	2,90
L1210	H	Ethyl (R-isomer)	H	n-Heptyl	4,04
MCF-7	H	Ethyl (R-isomer)	H	n-Heptyl	3,78
MDA-MB-231	H	Ethyl (R-isomer)	H	n-Heptyl	5,17
T24	H	Ethyl (R-isomer)	H	n-Heptyl	3,61
B16-F0	H	Ethyl (R-isomer)	Methoxy	Methoxy	>100
Caco-2	H	Ethyl (R-isomer)	Methoxy	Methoxy	>100
CHO	H	Ethyl (R-isomer)	Methoxy	Methoxy	>100
DU-145	H	Ethyl (R-isomer)	Methoxy	Methoxy	>100
HT-29	H	Ethyl (R-isomer)	Methoxy	Methoxy	>100
K562	H	Ethyl (R-isomer)	Methoxy	Methoxy	>100
L1210	H	Ethyl (R-isomer)	Methoxy	Methoxy	>100
MCF-7	H	Ethyl (R-isomer)	Methoxy	Methoxy	>100
MDA-MB-231	H	Ethyl (R-isomer)	Methoxy	Methoxy	>100
T24	H	Ethyl (R-isomer)	Methoxy	Methoxy	>100
B16-F0	H	Ethyl (S-isomer)	H	n-Heptyl	4,77
Caco-2	H	Ethyl (S-isomer)	H	n-Heptyl	6,32
CHO	H	Ethyl (S-isomer)	H	n-Heptyl	4,20
DU-145	H	Ethyl (S-isomer)	H	n-Heptyl	4,89
HT-29	H	Ethyl (S-isomer)	H	n-Heptyl	5,01

Cell line	R1	R2	R3	R4	G50 (μM)
K562	H	Ethyl (S-isomer)	H	n-Heptyl	3,59
L1210	H	Ethyl (S-isomer)	H	n-Heptyl	5,67
MCF-7	H	Ethyl (S-isomer)	H	n-Heptyl	4,20
MDA-MB-231	H	Ethyl (S-isomer)	H	n-Heptyl	6,12
T24	H	Ethyl (S-isomer)	H	n-Heptyl	3,93
B16-F0	H	Ethyl (S-isomer)	H	n-Hexyloxy	8,26
Caco-2	H	Ethyl (S-isomer)	H	n-Hexyloxy	9,50
CHO	H	Ethyl (S-isomer)	H	n-Hexyloxy	3,28
DU-145	H	Ethyl (S-isomer)	H	n-Hexyloxy	9,46
HT-29	H	Ethyl (S-isomer)	H	n-Hexyloxy	8,12
K562	H	Ethyl (S-isomer)	H	n-Hexyloxy	3,88
L1210	H	Ethyl (S-isomer)	H	n-Hexyloxy	7,42
MCF-7	H	Ethyl (S-isomer)	H	n-Hexyloxy	10,41
MDA-MB-231	H	Ethyl (S-isomer)	H	n-Hexyloxy	8,75
T24	H	Ethyl (S-isomer)	H	n-Hexyloxy	7,16
B16-F0	H	Ethyl (S-isomer)	Methoxy	Methoxy	>100
Caco-2	H	Ethyl (S-isomer)	Methoxy	Methoxy	>100
CHO	H	Ethyl (S-isomer)	Methoxy	Methoxy	>100
DU-145	H	Ethyl (S-isomer)	Methoxy	Methoxy	>100
HT-29	H	Ethyl (S-isomer)	Methoxy	Methoxy	>100
K562	H	Ethyl (S-isomer)	Methoxy	Methoxy	>100
L1210	H	Ethyl (S-isomer)	Methoxy	Methoxy	>100
MCF-7	H	Ethyl (S-isomer)	Methoxy	Methoxy	>100
MDA-MB-231	H	Ethyl (S-isomer)	Methoxy	Methoxy	>100
T24	H	Ethyl (S-isomer)	Methoxy	Methoxy	>100
B16-F0	H	H	H	Cyclohexyl	7,77
Caco-2	H	H	H	Cyclohexyl	9,37
CHO	H	H	H	Cyclohexyl	6,16
DU-145	H	H	H	Cyclohexyl	9,09
HT-29	H	H	H	Cyclohexyl	8,78
K562	H	H	H	Cyclohexyl	7,12
L1210	H	H	H	Cyclohexyl	6,94
MCF-7	H	H	H	Cyclohexyl	10,73
MDA-MB-231	H	H	H	Cyclohexyl	9,17
T24	H	H	H	Cyclohexyl	7,57
B16-F0	H	H	H	n-Heptyl	5,37
Caco-2	H	H	H	n-Heptyl	8,07
CHO	H	H	H	n-Heptyl	5,39

Cell line	R1	R2	R3	R4	G50 (μM)
DU-145	H	H	H	n-Heptyl	7,16
HT-29	H	H	H	n-Heptyl	4,90
K562	H	H	H	n-Heptyl	3,85
L1210	H	H	H	n-Heptyl	4,59
MCF-7	H	H	H	n-Heptyl	8,62
MDA-MB-231	H	H	H	n-Heptyl	7,87
T24	H	H	H	n-Heptyl	3,41
B16-F0	H	H	H	n-Hexyloxy	5,38
Caco-2	H	H	H	n-Hexyloxy	8,42
CHO	H	H	H	n-Hexyloxy	5,35
DU-145	H	H	H	n-Hexyloxy	12,41
HT-29	H	H	H	n-Hexyloxy	6,95
K562	H	H	H	n-Hexyloxy	5,13
L1210	H	H	H	n-Hexyloxy	5,99
MCF-7	H	H	H	n-Hexyloxy	9,88
MDA-MB-231	H	H	H	n-Hexyloxy	10,18
T24	H	H	H	n-Hexyloxy	4,28
B16-F0	H	H	Methoxy	Methoxy	35,33
Caco-2	H	H	Methoxy	Methoxy	>100
CHO	H	H	Methoxy	Methoxy	33,05
DU-145	H	H	Methoxy	Methoxy	48,22
HT-29	H	H	Methoxy	Methoxy	18,98
K562	H	H	Methoxy	Methoxy	5,14
L1210	H	H	Methoxy	Methoxy	19,82
MCF-7	H	H	Methoxy	Methoxy	48,97
MDA-MB-231	H	H	Methoxy	Methoxy	>100
T24	H	H	Methoxy	Methoxy	20,59
B16-F0	H	Methyl (R-isomer)	H	n-Heptyl	3,79
Caco-2	H	Methyl (R-isomer)	H	n-Heptyl	4,94
CHO	H	Methyl (R-isomer)	H	n-Heptyl	3,46
DU-145	H	Methyl (R-isomer)	H	n-Heptyl	3,63
HT-29	H	Methyl (R-isomer)	H	n-Heptyl	2,17
K562	H	Methyl (R-isomer)	H	n-Heptyl	2,41
L1210	H	Methyl (R-isomer)	H	n-Heptyl	2,42
MCF-7	H	Methyl (R-isomer)	H	n-Heptyl	3,31
MDA-MB-231	H	Methyl (R-isomer)	H	n-Heptyl	4,64
T24	H	Methyl (R-isomer)	H	n-Heptyl	2,18
B16-F0	H	Methyl (R-isomer)	H	n-Hexyloxy	6,38

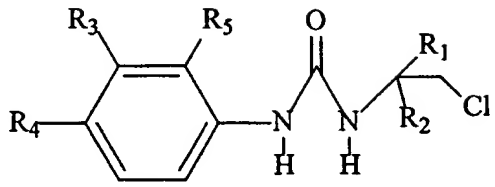
Cell line	R1	R2	R3	R4	G50 (μM)
Caco-2	H	Methyl (R-isomer)	H	n-Hexyloxy	8,57
CHO	H	Methyl (R-isomer)	H	n-Hexyloxy	2,63
DU-145	H	Methyl (R-isomer)	H	n-Hexyloxy	13,24
HT-29	H	Methyl (R-isomer)	H	n-Hexyloxy	9,55
K562	H	Methyl (R-isomer)	H	n-Hexyloxy	2,68
L1210	H	Methyl (R-isomer)	H	n-Hexyloxy	6,21
MCF-7	H	Methyl (R-isomer)	H	n-Hexyloxy	8,30
MDA-MB-231	H	Methyl (R-isomer)	H	n-Hexyloxy	10,48
T24	H	Methyl (R-isomer)	H	n-Hexyloxy	7,14
B16-F0	H	Methyl (R-isomer)	Methoxy	Methoxy	26,44
Caco-2	H	Methyl (R-isomer)	Methoxy	Methoxy	>100
CHO	H	Methyl (R-isomer)	Methoxy	Methoxy	32,16
DU-145	H	Methyl (R-isomer)	Methoxy	Methoxy	34,92
HT-29	H	Methyl (R-isomer)	Methoxy	Methoxy	14,76
K562	H	Methyl (R-isomer)	Methoxy	Methoxy	9,62
L1210	H	Methyl (R-isomer)	Methoxy	Methoxy	10,34
MCF-7	H	Methyl (R-isomer)	Methoxy	Methoxy	25,13
MDA-MB-231	H	Methyl (R-isomer)	Methoxy	Methoxy	43,58
T24	H	Methyl (R-isomer)	Methoxy	Methoxy	12,37
B16-F0	H	Methyl (S-isomer)	H	n-Heptyl	6,60
Caco-2	H	Methyl (S-isomer)	H	n-Heptyl	7,61
CHO	H	Methyl (S-isomer)	H	n-Heptyl	3,80
DU-145	H	Methyl (S-isomer)	H	n-Heptyl	7,46
HT-29	H	Methyl (S-isomer)	H	n-Heptyl	7,69
K562	H	Methyl (S-isomer)	H	n-Heptyl	6,96
L1210	H	Methyl (S-isomer)	H	n-Heptyl	7,48
MCF-7	H	Methyl (S-isomer)	H	n-Heptyl	5,56
MDA-MB-231	H	Methyl (S-isomer)	H	n-Heptyl	8,33
T24	H	Methyl (S-isomer)	H	n-Heptyl	6,15
B16-F0	H	Methyl (S-isomer)	H	n-Hexyloxy	8,45
Caco-2	H	Methyl (S-isomer)	H	n-Hexyloxy	7,98
CHO	H	Methyl (S-isomer)	H	n-Hexyloxy	3,66
DU-145	H	Methyl (S-isomer)	H	n-Hexyloxy	12,55
HT-29	H	Methyl (S-isomer)	H	n-Hexyloxy	10,50
K562	H	Methyl (S-isomer)	H	n-Hexyloxy	7,48
L1210	H	Methyl (S-isomer)	H	n-Hexyloxy	8,20
MCF-7	H	Methyl (S-isomer)	H	n-Hexyloxy	7,99
MDA-MB-231	H	Methyl (S-isomer)	H	n-Hexyloxy	9,08

Cell line	R1	R2	R3	R4	G50 (μM)
T24	H	Methyl (S-isomer)	H	n-Hexyloxy	9,93
B16-F0	H	Methyl (S-isomer)	Methoxy	Methoxy	>100
Caco-2	H	Methyl (S-isomer)	Methoxy	Methoxy	>100
CHO	H	Methyl (S-isomer)	Methoxy	Methoxy	>100
DU-145	H	Methyl (S-isomer)	Methoxy	Methoxy	>100
HT-29	H	Methyl (S-isomer)	Methoxy	Methoxy	>100
K562	H	Methyl (S-isomer)	Methoxy	Methoxy	>100
L1210	H	Methyl (S-isomer)	Methoxy	Methoxy	>100
MCF-7	H	Methyl (S-isomer)	Methoxy	Methoxy	>100
MDA-MB-231	H	Methyl (S-isomer)	Methoxy	Methoxy	>100
T24	H	Methyl (S-isomer)	Methoxy	Methoxy	>100
B16-F0	H	Propyl (racemic mixture)	H	Cyclohexyl	4,14
Caco-2	H	Propyl (racemic mixture)	H	Cyclohexyl	6,04
CHO	H	Propyl (racemic mixture)	H	Cyclohexyl	2,12
DU-145	H	Propyl (racemic mixture)	H	Cyclohexyl	4,30
HT-29	H	Propyl (racemic mixture)	H	Cyclohexyl	3,03
K562	H	Propyl (racemic mixture)	H	Cyclohexyl	4,93
L1210	H	Propyl (racemic mixture)	H	Cyclohexyl	4,12
MCF-7	H	Propyl (racemic mixture)	H	Cyclohexyl	5,05
MDA-MB-231	H	Propyl (racemic mixture)	H	Cyclohexyl	6,37
T24	H	Propyl (racemic mixture)	H	Cyclohexyl	4,24

Although the invention has been described above with respect with one specific form, it will be evident to a person skilled in the art that it may be modified and refined in various ways. It is therefore wished to have it understood that the present invention should not be limited in scope, except by the terms of the following claims.

I claim:

1. A compound of formula:

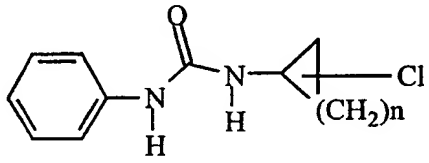


wherein

R_1 is C_1-C_6 lower alkyl, C_3-C_7 cycloalkyl, C_1-C_6 lower alkoxy, C_1-C_6 hydroxy alkyl, or C_1-C_6 lower halide;

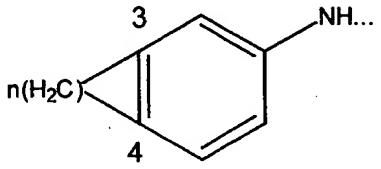
R_2 is H, C_1-C_6 lower alkyl, C_3-C_7 cycloalkyl, C_1-C_6 lower alkoxy, C_1-C_6 hydroxy alkyl or C_1-C_6 lower halide, di-halide or tri-halide;

R_1 and R_2 may also be part of cyclic structures expressed by the formula:



n= 1 to 6

R_3 and R_4 are as defined in R_5 or halide, di-halide, trihalide, C_1-C_7 lower dialkyl, or alicyclic groups of the following structure



wherein n = 2 to 8 carbon atoms, said alicyclic ring can be substituted by one or more groups as defined in R_5;

or polycyclic rings bearing not more than three rings wherein the rings other than the ring bearing the substituted 2-chloroethylamino moiety can be substituted by one or more groups as defined in R_5;

R_5 is H, C_1-C_7 lower alkyl, C_1-C_7 lower alkoxy, C_1-C_7 hydroxy alkyl, C_1-C_7 amino alkyl, C_1-C_6 thio alkyl, C_1-C_5 S-lower alkyl, C_1-C_7 N-lower alkyl, C_1-C_7 N,N-dilower alkyl, C_1-C_7 lower cyanoalkyl, C_1-C_7 lower haloalkyl, C_1-C_7 lower sulfoxide or C_3-C_7 cycloalkyl;
or a prodrug thereof.

2. A compound of claim 1 wherein R_2 is R-ethyl or R-propyl.

3. A compound of claim 2 wherein R_4 is Iodine.

4. A compound of claim 2 wherein R_5 is selected from secbutyl, tertbutyl and isopropyl.

5. A compound of claim 1 wherein R_3 and R_4 are methyl.

6. A compound of any of claims 1 to 5 wherein the compound is essentially pure R-isomer form.

7. A pharmaceutical composition comprising the compound of any of claims 1 to 6 and a pharmaceutically acceptable carrier.

8. A medicament for use in treating cancer comprising the compound of any of claims 1 to 6 and a pharmaceutically acceptable carrier.

9. The use of the compound of any of claims 1 to 6 for the treatment of cancer.